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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/917,384	07/28/2001	William S. Adney	NREL 01-38	9964

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,384	ADNEY ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,17-21,23-25,28,30-35,44,45 and 69-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 14, 17-21, 23-25, 28, 30-35, 44-45, 69-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 14, 17-21, 23-25, 28, 30-35, 44-45, 69-84, are currently at issue and are present for examination.

Applicants' amendments and arguments filed on 4-18-06, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Sequence Compliance

It is noted that applicant has filed a sequence listing on 9-6-05. However, it is not clear to the Examiner as to why the sequence listing was filed now and whether said sequence listing is identical to that filed previously on 1-8-02 or whether said sequence listing is an amended version. Examiner requests a clarification as to why this sequence listing has been filed and a statement from the applicant that the newly filed sequence listing is identical in all respects to the sequence listing filed earlier on 1-8-02.

In response to the previous Office action, applicants submit that there is no difference between the sequence listing filed on 9-6-05 and that filed on 11-27-02. However, Examiner has now discovered that applicants had indeed filed a sequence listing previous to 11-27-02 and it is not clear to the Examiner whether there are any differences between the sequence listing filed on 9-6-05 and that filed on 1-8-02. Examiner requests clarification.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-9, 14, 17-21, 23-25, 69-78 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-9, 14, 17-21, 23-25, 69-78 are all drawn to "a composition comprising a protein..." which reads on a product of nature. Claims directed to products of nature are considered to contain non-statutory subject matter. Examiner suggests amending the claims to read "a composition comprising an isolated or purified protein.." showing the hand of man to overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 9, 14, 17-21, 28, 30-35, 44-45, 75, 79-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-5, 9, 14, 17-21, 28, 30-34, 44-45, 75, 79-80 are drawn to polypeptide sequences that are "about 95%" or "about 98%" identical to SEQ ID NO:1, 2, 4, 5, 6, 7. However, a perusal of the specification indicates that applicants have no support for the newly added language which now constitutes a "new matter". Therefore claims 1-5, 9, 14, 17-21, 28, 30-34, 44-45, 75, 79-80 are rejected for introducing "new matter" into the claims. A perusal of the specification indicated support for only "90% identity" language and that too for only SEQ ID NO:1 (page 18 of the specification).

However, Examiner was unable to find the support for either " about 95%" or " about 98% identity" language for either SEQ ID NO:1 or for the other sequences.

In response to the previous Office action, applicants have traversed the above rejection and argue that the specification fully supports the new language in the claims. Applicants quote from the MPEP the court decision of *In re Wertheim*. However, they fail to explain as to how the fact pattern of the that case applies to the instant situation. Examiner maintains that the fact pattern of the example in the MPEP and that in the instant application are quite different. Applicants maintain that the original specification as filed teaches that Guxl polypeptides of the invention are preferably at least 60%, 70%, or 90% in some embodiments, identical to SEQ ID NO: 1 (See lines 39-41 of page 18 of the specification) and it also teaches that "Gux1 polypeptides of the invention include isolated polypeptides having an amino acid sequence as shown below in Example 1; Table 1 and in SEQ ID NO: 1, as well as variants and derivatives, including fragments, having substantial identity to the amino acid sequence of SEQ ID NO: 1 and that retain any of the functional activities of Guxl" (Lines 25-28 of page 17 of the specification). Applicants also argue that the specification teaches that, "Guxl polypeptide fragments may include, but are not limited to, the polypeptide sequences listed in Table 4, SEQ ID NOS: 3, 4, 5, 6, and 7." (Lines 9-10 of page 19) and therefore the instant specification teaches polypeptides that are at least 60% identical to SEQ ID NOS: 1, 3, 4, 5, 6, and 7. Applicants continue to maintain since, polypeptides that are 100% identical to SEQ ID NOS: 1,3, 4, 5, 6, and 7 have been disclosed in the specification one of skill in the art would recognize that Applicants had possession of polypeptides that have between 60% to 100% sequence identity with SEQ ID NOS: 1, 3; 4, 5, 6, and 7 at the time the application was filed and that both 95% and

98% fall between the range of 60% to 100%. Examiner respectfully disagrees with such an argument. Applicants are assuming information that is not explicit in the specification. Unless and until the specification clearly defines that polypeptides that are 95% and 98% identical to a given sequence having a specific SEQ ID NO and a clear definition as to what applicants intend by the language "about 95%" or "about 98%", it cannot be concluded that the specification provides support for such language. Therefore the above rejection is maintained.

Claims 1-6, 14, 17-21, 23-25, 28-35, 44-45, 69-75, 79, 81, 84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Gux 1 polypeptide comprising the specific catalytic domain of an exoglucanase, i.e., full length SEQ ID NO:5 or a polypeptide comprising an amino acid sequence 98% identical to SEQ ID NO:5, further comprising a CBD-III domain with SEQ ID NO:4 or an amino acid sequence that is 98% identical to SEQ ID NO:4 and a CBD-II domain with SEQ ID NO:7 or an amino acid sequence that is 98% identical to SEQ ID NO:7, or a peptide having SEQ ID NO:1 or an amino acid sequence that is 98% identical to SEQ ID NO:1 having the specific catalytic activity of an exoglucanase encoded by a nucleic acid sequence with SEQ ID NO:2, does not reasonably provide enablement for any or all such Gux I peptide comprising 1) any catalytic domain of the GH48 family hydrolase with any 637 to about 643 amino acids in length or 2)any or all CBDIII domain that is about 150-156 amino acids in length including variants and mutants that are 95% identical to SEQ ID NO:4 or 3) any CBDII domain that is 95-105 amino acids in length including variants and mutants that are 95% identical to SEQ ID NO:7 or 4) an amino acid sequence with exoglucanase activity which is 95% identical to SEQ ID NO:1 encoded by a

polynucleotide that is 95% identical to SEQ ID NO:2, or 5) a Gux1 peptide comprising any GH48 family catalytic domain and an amino acid sequence that is 95% identical to SEQ ID NO:5 or comprising only amino acids 359-418 of SEQ ID NO:5 or 6)a peptide comprising amino acid sequence that is 90% or at least 98% identical to SEQ ID NO:4, 5, 6, 7 or 1 (without any attached function of such polypeptides), or 7)fusion polypeptides of the above polypeptides comprising a heterologous polypeptide such a peptide tag, or a substrate targeting moiety or leucine zipper or a composition comprising such polypeptides along with a carrier (without any attached function of such polypeptides). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-6, 14, 17-21, 23-25, 28-35, 44-45, 69-75, 79, 81, 84 are so broad as to encompass any polypeptide with exoglucanase function and/or a polypeptide comprising any CBDIII domain that is about 150-156 amino acids in length or any CBDII domain that is 95-105 amino acids in length or an amino acid sequence encoded by a polynucleotide that is 95% identical to SEQ ID NO:2, or a Gux1 peptide comprising any GH48 family catalytic domain and an amino acid sequence that is 95% identical to SEQ ID NO:5 or a peptide comprising amino

acid sequence that is 95% identical to SEQ ID NO:4, 5, 6, 7 or 1 and having exoglucanase activity, or fusion polypeptides of the above polypeptides comprising a heterologous polypeptide such a peptide tag, or a substrate targeting moiety or leucine zipper or a composition comprising such polypeptides along with a carrier.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of Gux1 polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one such Gux1 having an amino acid sequence, SEQ ID NO:1 or 5, encoded by polynucleotide SEQ ID NO:2, wherein the polypeptide has a specific activity, beta 1-4 exoglucanase activity which also comprises CBD domains having the amino acid sequence SEQ ID NO:4 or 7. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides some even with an undefined function/activity. The specification is limited to teaching use of SEQ ID NO: 1 or a polypeptide comprising polypeptides with SEQ ID NO:4, 5 and 7 as a Gux1 polypeptide with exoglucanase activity but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working

examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any glycosylhydrolase polypeptide as described in the above paragraphs because the specification does not establish: (A) regions of the protein structure which may be modified without effecting either the exoglucanase catalytic activity or the cellulose binding activity of the CBD domains; (B) the general tolerance of exoglucanase such as cellulase or endoglucanases and the CBDs to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any exoglucanase or any CBD polypeptide amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including exoglucanase catalytic domains, and cellulose binding domains with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants argue that Examiner has acknowledged that the instant specification is enabling for a Gux 1 polypeptide comprising the GH48 catalytic domain and carbohydrate binding domains II and III having 98% sequence identity with the respective domain sequences disclosed in the specification. Applicants also submit that Examiner has also stated that the instant specification is enabling for a polypeptide having SEQ ID NO: 1 or an amino acid sequence that is 98% identical to SEQ ID NO: 1 having the catalytic activity of an exoglucanase and therefore they have now amended all claims such that all claims now recite a polypeptide having catalytic activity of an exoglucanase and containing at least one of the three domains selected from GH48 catalytic domain and carbohydrate binding domains II and III, or their variants thereof with about 95% sequence identity to the specific sequence disclosed in the Specification. Examiner respectfully disagrees with such an argument. Examiner had only agreed in the previous Office action that claims are enabled for a polypeptide having exoglucanase activity wherein said polypeptide comprises the

amino acid sequence SEQ ID NO:5 or a sequence that is 98% identical to SEQ ID NO:5 for catalytic activity and SEQ ID NO:4 and 7 or a sequence that is 98% identical to SEQ ID NO:4 and 7 for the CBD domains, but not that the claims are enabled for polypeptides comprising sequences that are 95% identical to any of the SEQ ID Nos. Applicants have confused the suggestion/guidance provided by the Examiner to address the "written description" rejection for enablement rejection and argue that they have changed the sequence identity from 98% to 95% in some instances and refer to Examples 13 and 14 of the Guidelines for Written Description. However, such amendments have overcome the written description rejection but does not address the enablement rejection. Therefore, Examiner continues to maintain the enablement rejection since applicants have not addressed the rejection as it applies to CBD domains as well as claims directed to polypeptides comprising 95% identical amino acid sequences.

Claims 1, 5, 6, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5, 6 are directed to composition comprising a Gux1 peptide wherein said Gux1 peptide comprises a catalytic domain GH48 family exoglucanase comprising SEQ ID NO:5 and a carbohydrate binding domain CBD type III of 150-156 amino acids in length and a CBD type II of 95-105 amino acids in length and fusion polypeptides of the same fused to heterologous polypeptides all of which encompass variants, mutants and recombinants. Claims 1,5,6, are rejected under this section of 35 USC 112 because the claims are directed to a genus of

polypeptides comprising modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue (i.e., variants and mutants) that have not been disclosed in the specification. No description has been provided of even a representative number of polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQID NO:4 and 7 as CBD domains, has been provided by applicants which would indicate that they had possession of the claimed genus of all the polypeptides. The specification does not contain any disclosure of the specific structure of the polypeptide sequences, including fragments and variants within the scope of the claimed genus or identifying information that the structure of SEQ ID NO:4 and 7 is representative of all the species claimed herein. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only one species of each CBD which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have claims to incorporate the structure of the polypeptides. However, Applicants have failed to address the structure of CBD as claimed in claims 1, 5 and 9. Therefore the above rejection is maintained.

Claims 81-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of polypeptides having exoglucanase activity and comprising amino acids 359-418 of SEQ ID NO:5 or five or fewer conservative amino acid substitutions in amino acids 359-418 of SEQ ID NO:5. The specification does not contain any disclosure of the structure of amino acid sequences included in the claimed genera. The genus of sadi polypeptides claimed is a large variable genus having many different structures. Therefore, many structurally disticnt polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e., full length of SEQ ID NO:5) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypetides defined by sequence or a recitation of structural features common to members of the genus, **which features constitute a substantial portion of the genus**. The recited structural feature of the genus (i.e., polypeptide comprising a fragment of 59 amino acids of SEQ ID NO:5) does not constitute a substantial portion of the genus as the remainder of the structure of any polypeptide having exoglucanase activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Terminal Disclaimer

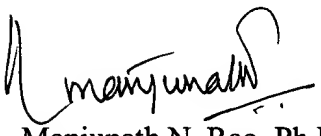
The terminal disclaimer filed on 4-18-06 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the patents issued for applications 09/917383 and 09/917378 has been reviewed and is accepted. The terminal disclaimer has been recorded. In view of the above TD the previous Obviousness Double patenting rejection is hereby withdrawn.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

October 18, 2006